General

Guideline Title

Pulmonary opportunistic infections. In: British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011.

Bibliographic Source(s)

Dockrell DH, Breen R, Lipman M, Miller RF. Pulmonary opportunistic infections. In: British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011. HIV Med. 2011 Sep;12(Suppl 2):25-42. [149 references]

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Level of evidence (I–IV) ratings are defined at the end of the "Major Recommendations" field.

General Overview

- While empirical therapy (usually directed against bacterial pathogens) may be appropriate for patients with CD4 counts >200 cells/µL, every effort should be made to confirm a specific diagnosis in the more immunocompromised individual (IV).

Pneumocystis jirovecii

Diagnosis

- It is important to obtain either tissue samples or body fluid in which the organism can be identified (III).
- In view of the current reduction in *Pneumocystis jirovecii* pneumonia (PCP) presentations, all cases should undergo investigation and not just receive treatment empirically for presumed PCP (IV).
- Currently, no definitive recommendations concerning nucleic acid amplification techniques (NAAT)-based assays can be made. Where centres use them as part of a diagnostic algorithm they must be interpreted with input from the testing laboratory in the light of their sensitivity and specificity. They should be combined with a definitive visualization technique (IV).

Treatment

- First-line treatment for moderate–severe PCP (partial pressure of oxygen in arterial blood [PaO_2] ≤9.3 kPa [≤70 mmHg]) is with high-dose intravenous (iv) trimethoprim-sulphamethoxazole for 21 days (cotrimoxazole, TMP-SMX) (Ib).
- Some clinicians will continue with iv therapy for the duration; many switch individuals showing a good initial response to oral therapy at doses equivalent to those used for mild–moderate severity disease (IV).
- Oral or iv corticosteroids should be started in all cases of suspected moderate–severe PCP with a PaO_2<9.3 kPa (<70 mmHg) or oxygen saturation (SpO_2) <92% (Ib).
- First-line treatment for mild–moderate disease (PaO_2 >9.3 kPa [>70 mmHg]) is with oral TMP-SMX (Ib).
- There is currently no evidence to support the routine determination of dihydropteroate synthase (DHPS) mutations; or that if they are detected early in treatment, patients should not receive TMP-SMX (III).
- Glucose 6-phosphate dehydrogenase deficiency (G6PD) levels should be checked prior to TMP-SMX, dapsone or primaquine use (IV)
- At a minimum, mechanical ventilation should be undertaken in patients who deteriorate early in treatment, or who have good functional status documented prior to the acute respiratory episode (Walzer et al., 2008) (III).

Prophylaxis

- PCP prophylaxis should be used in all human immunodeficiency virus (HIV)-seropositive individuals with a CD4 T-cell count persistently <200 cells/μL, or a CD4 T-cell percentage of all lymphocytes <14%, or oral candidiasis or previous acquired immunodeficiency syndrome (AIDS)-defining illness (Schneider et al., 1992) (Ib).
- TMP-SMX is the agent of choice. Although other agents may have similar efficacy against PCP, they do not provide the additional protection provided by TMP-SMX against other infections and some are not as effective at low CD4 T-cell counts (Ib).

Impact of Highly Active Antiretroviral Therapy (HAART)

- Early initiation of HAART is favoured in individuals with PCP (IIb).
- Individuals with CD4 T-cell counts >200 cells/μL for more than 3 months can discontinue PCP prophylaxis (Ib).

Bacterial Pneumonia

Presentation

- Where a purulent sputum sample can be obtained prior to the first dose of antibiotics, this should be sent for Gram stain and culture to guide therapy. In cases requiring hospitalization, a blood culture should also be obtained (IV).

Treatment

- HIV-seropositive individuals with community-acquired pneumonia should be treated as per HIV-seronegative populations (IV).

Cryptococcus neoformans

Treatment

- Pulmonary cryptococcosis is usually treated as per central nervous system (CNS) infection (III).
- Pulmonary cryptococcosis, when focal and not associated with hypoxia or positive cerebrospinal fluid (CSF) exam, may be treated initially with fluconazole 400 mg once daily (od) (III).
- In cases with pulmonary cryptococcosis a CSF examination should be performed to determine whether meningitis is present (III).
- If the CSF exam is negative, and (1) there is no other evidence of dissemination, (2) radiological infiltrates are focal and (3) there is no hypoxia, treatment with fluconazole, 400 mg od for the initial 10 weeks and 200 mg od by mouth (po) after this, is an alternative strategy (Meyohas et al., 1995) (III).

See the "*Cryptococcus neoformans*" section of the National Guideline Clearinghouse (NGC) summary of the British HIV Association and British Infection Association guideline Central nervous system opportunistic infections. In: British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011 for recommendations on prophylaxis and impact of HAART.

Aspergillosis

Diagnosis

- Special fungal stains such as KOH stains of sputum or bronchoalveolar lavage (BAL) and Grocott–Gomori methenamine silver stains or

equivalents on biopsy specimens should be obtained on all respiratory specimens from HIV-seropositive individuals with pulmonary syndromes of undetermined aetiology (IV).
- Fungal cultures should be requested on all samples as the definitive method of proving speciation (IV).

Treatment

- On the basis of trials involving largely HIV-seronegative individuals, but including small numbers of HIV-seropositive individuals, primary therapy for invasive pulmonary aspergillosis is with voriconazole (Herbrecht et al., 2002) (IV).

Prophylaxis

- Routine prophylaxis for pulmonary aspergillosis is not warranted (IV).

Cytomegalovirus (CMV)

Diagnosis

- Diagnosis of CMV pneumonia requires a biopsy specimen to provide evidence of pulmonary involvement in association with a compatible clinical syndrome (III).

Treatment

- The majority of individuals in whom microbiological tests on BAL, or biopsy, demonstrate CMV should not receive treatment for CMV (III).
- Cases with a compatible clinical syndrome, positive microbiology for CMV in BAL or biopsy and positive histology on biopsy or BAL without an alternative microbiological cause of respiratory disease should receive anti-CMV treatment (III).
- In co-infected individuals it is reasonable to start by treating the co-pathogen first and to only treating the CMV if there is a failure of clinical response (IV).
- Standard therapy for CMV pneumonitis is with ganciclovir (III).

Prophylaxis

- Valganciclovir prophylaxis (900 mg od or 2 times a day [bd]) can be considered in selected individuals when the CD4 count remains <50 cells/μL, there is persistent detection of CMV deoxyribonucleic acid (DNA) or CMV viraemia, coupled with a low risk of prompt immune reconstitution by HAART and there is no evidence of CMV end-organ disease (IV), since detection of CMV DNA is a risk factor for death in this setting over and above the risk of low CD4 T-cell count or HIV viraemia (Wohl et al., 2005).
- Valganciclovir may be considered as primary prophylaxis in selected patients with persistent immunosuppression and detectable CMV DNA; or as secondary prophylaxis in those with relapse of CMV pneumonia after appropriate primary therapy (IV).

Influenza A Virus (IAV)

Treatment

- HIV-seropositive individuals should receive the neuraminidase inhibitor oseltamivir (assuming the majority of circulating strains in a given flu season show susceptibility) (IV).

Prevention

- HIV-seropositive individuals should receive IAV vaccination each year (Ib).
- When oseltamivir was prescribed it significantly shortened the duration of shedding, therefore IAV treatment may reduce secondary transmission in HIV-seropositive individuals, regardless of symptoms and treatment of index cases may be considered as a preventative measure (IV).
- For individuals who are (1) significantly immunosuppressed (CD4 T-cell count <200 cells/mL), (2) have not received vaccination or are believed to be at significant risk of vaccine non-response due to either immunosuppression or recent administration and (3) have been exposed within the last 48 h, antiviral prophylaxis may be considered although there are no HIV-specific data currently on which to base this recommendation (IV).

Definitions:

Level of Evidence

Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well designed quasi-experimental study
III	Evidence obtained from well designed non-experimental descriptive studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Pulmonary opportunistic infections
  - *Pneumocystis jirovecii* pneumonia (PCP)
  - Bacterial pneumonia
  - Fungal pneumonia (cryptococcosis, aspergillosis)
  - Cytomegalovirus (CMV) infection
  - Influenza A virus (IAV) infection (flu)
- Human immunodeficiency virus (HIV) seropositivity

Guideline Category

Diagnosis

Management

Prevention

Risk Assessment

Treatment

Clinical Specialty

Infectious Diseases

Internal Medicine

Pathology

Preventive Medicine

Pulmonary Medicine

Radiology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To help physicians in the United Kingdom investigate and manage human immunodeficiency virus (HIV)-seropositive patients suspected of or having a pulmonary opportunistic infection

Target Population

Human immunodeficiency virus (HIV)-seropositive patients suspected of or having a pulmonary opportunistic infection

Interventions and Practices Considered

Diagnosis

1. *Pneumocystis jirovecii* pneumonia (PCP)
    - Obtaining tissue samples or body fluid in which the organism can be identified
    - Investigation of all suspected PCP cases before treatment
2. Bacterial pneumonia
    - Gram stain and culture of purulent sputum sample to guide therapy
    - Blood culture
3. Aspergillosis
    - Use of special fungal stains such as KOH stains of sputum
    - Bronchoalveolar lavage (BAL) and Grocott–Gomori methenamine silver stains or equivalents on biopsy specimens
    - Fungal cultures
4. Cytomegalovirus (CMV) infection
    - Biopsy specimen with evidence of pulmonary involvement
    - BAL
    - Evidence of compatible clinical syndrome

Treatment/Management/Prevention

1. PCP
    - High-dose intravenous (iv) trimethoprim-sulphamethoxazole (TMP-SMX)
    - Oral or iv corticosteroids
    - Routine determination of dihydropteroate synthase (DHPS) mutations (not recommended)
    - Checking glucose 6-phosphate dehydrogenase deficiency (G6PD) levels prior to TMP-SMX, dapsone, or primaquine use
    - Mechanical ventilation
    - TMP-SMX as agent of choice for prophylaxis
    - Early initiation of highly active antiretroviral therapy (HAART)
    - Discontinuation of HAART based on CD4 count
2. Bacterial pneumonia: treatment of community-acquired pneumonia as per human immunodeficiency virus (HIV)-seronegative populations
3. *Cryptococcus neoformans* infection
    - Treatment as per central nervous system (CNS) infection
    - Fluconazole
    - Cerebrospinal fluid (CSF) examination to determine whether meningitis is present
4. Aspergillosis
    - Voriconazole
    - Prophylaxis (not recommended)
5. CMV infection

- Ganciclovir
- Valganciclovir prophylaxis in selected individuals

6. Influenza A virus (IAV)
    - Oseltamivir
    - IAV vaccination every flu season
    - Antiviral prophylaxis

Major Outcomes Considered

- Sensitivity and specificity of diagnostic tests
- Relapse rate
- Response rate
- Morbidity and mortality
- Resolution of infection
- Adverse events related to therapy

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The PubMed database was searched under the following headings: HIV or AIDS and lung or pneumonia or pneumonitis and/or *Pneumocystis carinii*, *Pneumocystis jirovecii*, Pneumocystis pneumonia, PCP, *Cryptococcus neoformans*, cryptococci, *Cryptococcus, Aspergillus*, aspergillosis, CMV, influenza A virus, influenza B virus, parainfluenza virus, respiratory syncytial virus, bacteria and vaccination.

All information considered had to have been published in a peer review journal or presented at an international human immunodeficiency virus (HIV) meeting in abstract form. Inclusion/exclusion criteria essentially required that the information was relevant to the diagnosis, treatment or prevention of the specified opportunistic infection in HIV-positive individuals. Information of relevance to other related immunocompromised groups was also taken into consideration if the section authors felt relevant. Case reports were included and the review was not restricted only to clinical trials or meta-analyses. Search dates were from 1980 to January 2011.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence

Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial

IIa IIb	Evidence obtained from at least one well designed controlled study without randomization Evidence obtained from at least one other type of well designed quasi-experimental study
III	Evidence obtained from well designed non-experimental descriptive studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Not stated

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Not stated

Description of Method of Guideline Validation

Not applicable

Evidence Supporting the Recommendations

References Supporting the Recommendations

Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, Kern WV, Marr KA, Ribaud P, Lortholary O, Sylvester R, Rubin RH, Wingard JR, Stark P, Durand C, Caillot D, Thiel E, Chandrasekar PH, Hodges MR, Schlamm HT, Troke PF, de Pauw B, Invasive Fungal Infections Group of the European Organisation [trunc]. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002 Aug 8;347(6):408-15. PubMed

Meyohas MC, Roux P, Bollens D, Chouaid C, Rozenbaum W, Meynard JL, Poirot JL, Frottier J, Mayaud C. Pulmonary cryptococcosis: localized and disseminated infections in 27 patients with AIDS. Clin Infect Dis. 1995 Sep;21(3):628-33. PubMed

Schneider MM, Hoepelman AI, Eeftinck Schattenkerk JK, Nielsen TL, van der Graaf Y, Frissen JP, van der Ende IM, Kolsters AF, Borleffs JC. A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against Pneumocystis carinii pneumonia in patients with human immunodeficiency virus infection. The Dutch AIDS Treatment Group. N Engl J Med. 1992 Dec 24;327(26):1836-41. PubMed

Walzer PD, Evans HE, Copas AJ, Edwards SG, Grant AD, Miller RF. Early predictors of mortality from Pneumocystis jirovecii pneumonia in HIV-infected patients: 1985-2006. Clin Infect Dis. 2008 Feb 15;46(4):625-33. PubMed

Wohl DA, Zeng D, Stewart P, Glomb N, Alcorn T, Jones S, Handy J, Fiscus S, Weinberg A, Gowda D, van der Horst C. Cytomegalovirus viremia, mortality, and end-organ disease among patients with AIDS receiving potent antiretroviral therapies. J Acquir Immune Defic Syndr. 2005 Apr 15;38(5):538-44. PubMed

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Accurate diagnosis and appropriate treatment of pulmonary opportunistic infections in human immunodeficiency virus (HIV)-seropositive individuals

Potential Harms

- Adverse effects, including hypersensitivity and treatment-limiting toxicity, to drugs used to treat infections
- Refer to Table 3.6 in the original guideline document for potential interactions between drugs used in treatment of pulmonary opportunistic infections and antiretroviral drugs.
- Refer to Appendix 1 in the original guideline document for side effects of certain drug formulations.

Contraindications

Contraindications

- Refer to Table 3.6 in the original guideline document for potential contraindications for drugs used to treatment pulmonary opportunistic infections and antiretroviral drugs.
- Refer to Appendix 1 in the original guideline document for contraindications of certain drug formulations.

Qualifying Statements

Qualifying Statements

- These guidelines are primarily intended to guide practice in the United Kingdom and related health systems. Although it is hoped they can provide some guidance in developed countries there are some important distinctions in this environment and individual recommendations may not be as applicable in this setting.
- In the appendices in the original guideline document there is an A–Z of drugs used in the management of opportunistic infections. This is intended as a guideline but readers are advised to follow the discussion of dosing and the evidence for specific treatments provided in the text. In some cases alternative treatments are provided in the appendix in the original guideline document. These are not discussed in the text and these are mainly of historical interest and readers should be aware that these are not, in general, supported by the evidence base for treatments discussed in the text. It should also be noted that as evidence of drug toxicity, interactions, pregnancy risk and cost is rapidly evolving the table should be considered in association with the updated summary of product characteristics (SPC) for the agent and other relevant sources of drug information.
- Recommendations based upon expert opinion have the least evidence but perhaps provide an important reason for writing the guidelines: to produce a consensual opinion about current practice. It must, however, be appreciated that such opinion is not always correct and alternative practices may be equally valid. The recommendations contained in these guidelines should therefore be viewed as guidelines in the true spirit of the term. They are not designed to be restrictive nor should they challenge research into current practice. Similarly, although the British HIV Association (BHIVA) Opportunistic Infection Guidelines Group seeks to provide guidelines to optimize treatment, such care needs to be individualized and the authors have not constructed a document that they would wish to see used as a 'standard' for litigation.
- The clinical care of patients with known or suspected opportunistic infections (OIs) requires a multidisciplinary approach, drawing on the skills and experience of all healthcare professional groups. Moreover, these guidelines emphasize that inpatients with human immunodeficiency virus (HIV)-related disease often need rapid access to a variety of diagnostic tests and radiological interventions that may not be immediately available at local hospitals. Furthermore, expert interpretation of these tests by supporting specialties such as radiology, histopathology, microbiology and virology is often required. Optimal care of opportunistic infection can only be achieved by the close cooperation of these healthcare professionals and unless all are intimately involved in the care of patients, it is likely that the outcome will be less favourable. In keeping with BHIVA standards for HIV clinical care, patients needing inpatient care for HIV-related disease should ordinarily be admitted to an HIV centre or the relevant tertiary service in liaison with the HIV centre.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Mobile Device Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Identifying Information and Availability

Bibliographic Source(s)

Dockrell DH, Breen R, Lipman M, Miller RF. Pulmonary opportunistic infections. In: British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011. HIV Med. 2011 Sep;12(Suppl 2):25-42. [149 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Sep

Guideline Developer(s)

British HIV Association - Disease Specific Society

British Infection Association - Professional Association

Source(s) of Funding

British HIV Association

Guideline Committee

BHIVA Guidelines Writing Group on Opportunistic Infection

Composition of Group That Authored the Guideline

Section Authors: DH Dockrell, University of Sheffield, UK; R Breen, Royal Free Hospital, London, UK; M Lipman, Royal Free Hospital, London, UK; RF Miller, Mortimer Market Centre, London, UK

Group Joint Chair: Dr Mark Nelson, Chelsea & Westminster Hospital, London, UK

Group Joint Chair: Professor David Dockrell, University of Sheffield, UK

Group Joint Chair: Dr Simon Edwards, Mortimer Market Centre, London, UK

Writing Group Members: Dr Brian Angus, John Radcliffe Hospital, Oxford, UK; Dr Simon Barton, Chelsea & Westminster Hospital, London, UK; Dr Nick Beeching, Liverpool School of Tropical Medicine, UK; Prof Colm Bergin, St James's Hospital, Dublin, Ireland; Dr Marta Boffito, Chelsea & Westminster Hospital, London, UK; Dr Ronan Breen, Royal Free Hospital, London, UK; Dr Jonathan Cartledge, Mortimer Market Centre, London, UK; Dr Susan Clarke, St James's Hospital, Dublin, Ireland; Dr Martin Fisher, Brighton and Sussex University Hospital, Brighton, UK; Dr Andrew Freedman, Cardiff University School of Medicine, UK; Prof Brian Gazzard, Chelsea & Westminster Hospital, London, UK; Dr Alison Grant, London School of Hygiene and Tropical Medicine, UK; Dr Julia Greig, Royal Hallamshire Hospital, Sheffield, UK; Dr Rachael Jones, Chelsea & Westminster Hospital, London, UK; Prof Saye Khoo, University of Liverpool; Prof Clifford Leen, Edinburgh University, UK;

Dr Marc Lipman, Royal Free Hospital, London, UK; Dr Hadi Manji, National Hospital for Neurology & Neurosurgery, London, UK; Prof Robert Miller, Mortimer Market Centre, London, UK; Miss Suzanne Mitchell, Chelsea and Westminster Hospital, London, UK; Dr Ed Ong, Newcastle General Hospital, UK; Dr Anton Pozniak, Chelsea & Westminster Hospital, London, UK; Dr Matthias Schmid, Newcastle General Hospital, UK; Miss Marianne Shiew, Chelsea & Westminster Hospital, London, UK; Prof Mervyn Singer, University College London, UK; Dr Ed Wilkins, North Manchester General Hospital, UK; Dr Ian Williams, Royal Free and University College Medical School, London, UK; Dr Chris Wood, North Middlesex University Hospital, London, UK; Ms Rosy Weston, St Mary's Hospital, Imperial College, London, UK

Financial Disclosures/Conflicts of Interest

The British HIV Association (BHIVA) has a clear policy of declarations of interests within the Association:

- BHIVA requires that all members of guidelines writing groups, as well as any expert external peer reviewers, must declare all interests and membership of other committees retrospectively on an annual basis, to give protection to individuals working as members of writing groups.
- All members of guidelines writing groups must undertake a declaration of interests prior to serving on a writing group and this declaration is confirmed and repeated at the publication of each set of completed guidelines published.
- The details given in declaration forms are retained on a register at the Secretariat and can be made available for publication, if required.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the British HIV Association (BHIVA) Web site . Also available as a smartphone app from the BHIVA Web site .

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 30, 2014.

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